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Temporal Subtraction of Digital Breast Tomosynthesis Images for Improved
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14. ABSTRACT

The purpose of this project is to determine the feasibility of using temporal subtraction on Digital Breast Tomosynthesis (DBT) phantom images to allow for easier and earlier detection of breast cancer than with either technique alone. The ultimate goal of project would be applied to human subject data. Therefore, initial feasibility was tested on temporally spaced DBT images of human subjects. The investigator implemented a temporal subtraction algorithm using a rigid registration technique. However, the resulting subtraction showed many mis-registration errors likely due to differences in positioning and compression forces used during the temporally spaced acquisitions. This work has demonstrated that temporal subtraction of DBT images is most likely infeasible, although may be possible with fully 3D images such as dedicated breast CT data. The investigator is currently developing a 3D computer simulated breast phantom, a specific aim of proposal. Dedicated breast CT data was used as the basis for the phantom. In order to create the phantom, several methods are under development: an automated segmentation algorithm, a compression algorithm, and a simulated image acquisition algorithm. The phantom resulting from this work will combine the realism of empirical data with the flexibility of mathematical models. The phantom will incorporate information from breast models of several different human subjects and include the ability to change the breasts' size, composition, and compressibility.

15. SUBJECT TERMS
Digital Breast Tomosynthesis, Temporal Subtraction, Breast Imaging, Computer Simulation, Phantoms

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Introduction

This project is to decrease the number of breast cancers that are missed in conventional mammography by combining two methods developed to increase the sensitivity of breast cancer imaging: digital breast tomosynthesis (DBT) and temporal subtraction. The purpose of this project is to determine the feasibility of using temporal subtraction on DBT phantom images to allow for easier and earlier detection of breast cancer than with either technique alone. In addition, one of the specific aims for this project was to develop a realistic computer generated breast phantom. Computer phantoms are becoming an essential tool for use in medical imaging research. This necessity is because of the difficulty in obtaining real human data due to subject recruitment issues related to time and cost, as well as radiation dose considerations. Simulations can be used to study the imaging system design, acquisition protocols, reconstruction algorithms, and to evaluate image processing techniques. Computerized phantoms are advantageous because they can be modified in terms of size and tissue distribution, provide a "known truth" to aid in evaluating imaging devices and techniques, and do not require any additional material costs or production time other than software processing. One goal of this project is to create a breast phantom that can realistically simulate breast imaging data that is virtually indistinguishable from actual human breast data. The phantom will provide a vital tool to investigate current and emerging breast imaging methods and techniques with the ability to simulate realistic, predictive patient imaging data.

Body

Task 1. To generate tomosynthesis datasets of simulated and physical breast phantom: In progress:

1a. Develop a realistic computer simulated breast phantom simulation and generate up to 50 simulated tomosynthesis projection data with the phantom undergoing simulated tissue deformation.

At the time of the last report, the investigator believed that a combination of a mathematical and voxelized breast phantom would be the best path to pursue for the computer simulated phantom development. Using dedicated breast CT data[1, 2],[3] the investigator has developed an automated segmentation algorithm to classify the breast tissue and create a computer-simulated breast phantom. To the best of our knowledge, this will be the first breast phantom that combines the realism of high-resolution voxelized data with the flexibility of a mathematical phantom. This project has the potential to contribute significantly to breast imaging research for the advancements of detection techniques and technologies.

A denoising algorithm developed in our lab was used to process the projection images of the breast[4, 5]. The breast CT data was reconstructed using a custom written filtered back projection algorithm developed in our lab[4, 5]. The investigator developed an automated segmentation algorithm to classify the breast tissue into its different components: adipose, fibroglandular, and skin. Several steps were taken to accurately segment the data: post-reconstruction scatter correction, histogram classification, morphological operations, and fibroglandular compositional classification. Figure 1 shows an original axial slice of the breast CT data, an axial slice after denoising, and a segmented slice showing adipose tissue, skin, and 3 different levels of fibroglandular tissue representing different densities of fibroglandular tissue. The pectoral muscle was manually segmented with a method described previously[6].

Issues: The segmentation algorithm does not classify all tissue correctly; there are small regions missing fibroglandular tissue that was misclassified as adipose. However, the resulting segmentation provides an adequare representation of the breast necessary for phantom generation. Certain structures, such as Cooper's ligaments are not visible in the segmented data, and can be mathematically modeled and incorporated to enhance the realism of the breast model.
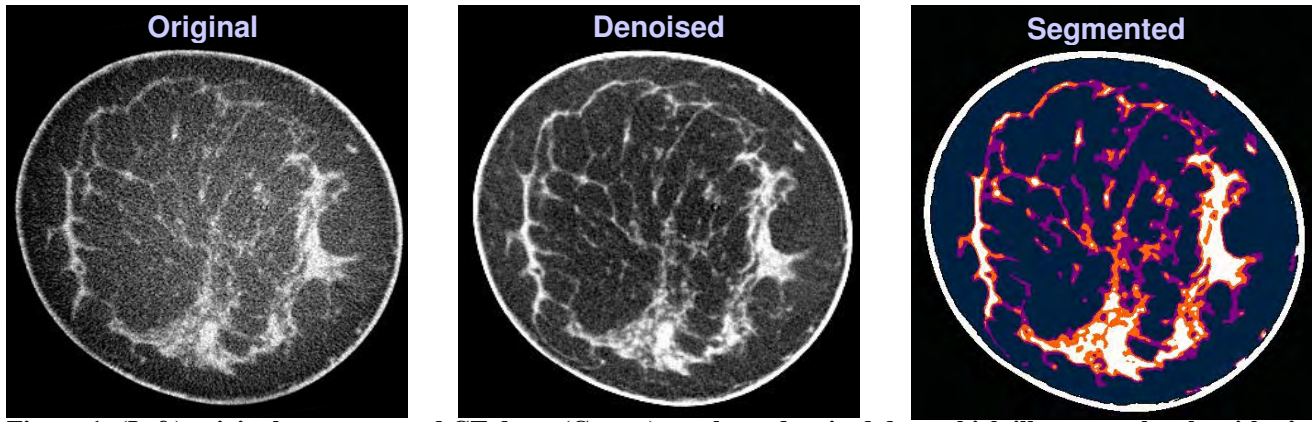
Figure 1: (Left) original reconstructed CT data; (Center) resultant denoised data which illustrates the algorithm's noise reduction capabilities; (Right) Segmented slice.

Computer graphics techniques are used to generate a 3D mesh surface model of the breast from the segmented data. In a mesh model, polygons are used to estimate the curved surfaces of the tissue. Once the mesh model is created, additional operations may be performed to manipulate or deform the mesh. After tissue classification a mesh surface model of a single breast was created for the different breast tissues using the matlab (Mathworks R2007A) *isosurface* function.
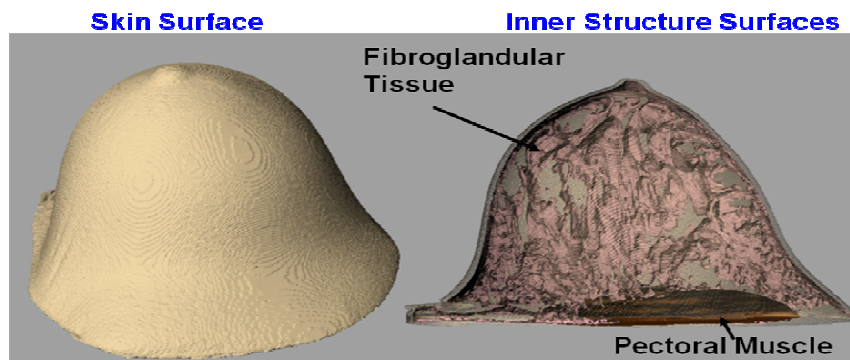

Figure 2: Graphical representation of the mesh model for the breast surface and inner structures.

Issues: The mesh algorithm of the breast may create some sub-sampling artifacts in the surface modeling, which may materialize in images acquired of the simulated breast. Smoothing the mesh may be implemented in the future if it does not reduce the resolution of the images.

In order to make the breast phantom applicable for research in these modalities, it is necessary to create a compression model component for the phantom. The breast is compressed during mammography and this is essential to produce high quality images. Breast compression optimizes image quality by reducing the breast thickness and therefore increases the visibility of small lesions. Compression also minimizes patient movement that would cause blurring effects in the resulting mammograms. Finally, x-rays pass through less breast thickness, resulting in reduced radiation dose.

We used a simplistic compression algorithm that did not account for the mechanical properties of different tissues. The breast was assumed to be incompressible and isotropic. Using the vertices locations in a single mesh model, the breast was compressed in one dimension and extended in the other dimensions in order to maintain the same volume and provide a simplistic simulated compression between stiff plates (Figure 3).
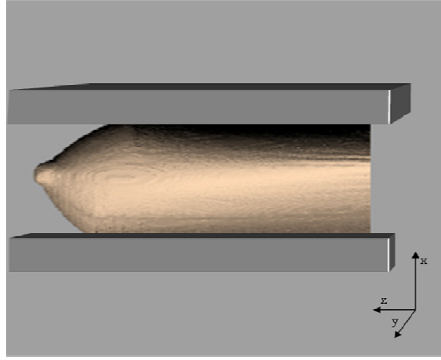
5

Figure 3: Graphical demonstration of simulated compression of the breast phantom.

Issues: The segmentation algorithm currently segments the breast into different breast components. However the algorithm does miss several small regions of fibroglandular tissue. The compression algorithm is too simplistic in its current implementation. In the future, we plan to investigate the use of finite element methods to simulate realistic compression. Finite-element methods will take into account the different mechanical properties of the breast tissues as well as the force distribution across the tissue due to compression.

1b. Acquire up to 30 tomosynthesis projections of a compressible and deformable physical phantom with physically simulated anatomy and under different simulated temporal discrepancies.

The mesh surface model was directly used for simulated mammogram acquisition. Segars et al. developed an analytic projection algorithm that can simulate parallel, fan, or cone-beam geometries directly from the mesh object[7]. Attenuation coefficients from the International Commission on Radiation Units and Measurements (ICRU) tissue data were used and a polyenergetic spectra used in mammography was modeled. Figure 4 shows, in addition, a slice from a simulated tomosynthesis acquisition of the phantom. An analytical noise free simulator was used to model the tomosynthsis image acquisition. The mesh model of the compressed breast was voxelized prior to simulated image acquisition.
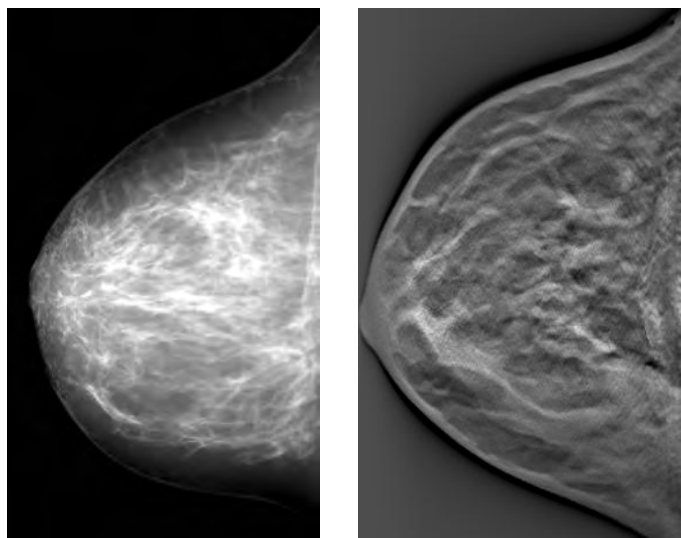

Figure 4: Simulated image acquisition of the breast phantom. (Left) Simulated mammogram; (Right) Simulated tomosynthesis slice.

The images in Figure 4 appear qualitatively realistic and these promising results from the simulated image acquisition of the breast phantom has demonstrated that more work needs to be performed on this task to develop the phantom further.

Issues: Voxelization of the breast model during the tomosynthesis acquisition was computationally extensive and resulted in lower resolution images. A tomosynthesis projection method that can work direction on the mesh model will be developed to improve resolution and decrease computational time.

Task 2+3. Develop and evaluate the temporal subtraction algorithm using simulated phantom images - Complete:

The investigator received IRB approval to use temporally acquired breast tomosynthesis datasets of two human patients. We developed an algorithm to register and subtract two clinical breast tomosynthesis datasets of the same patient that were acquired under IRB protocol with nine months temporal spacing. Calcification points common in the two image sets were used to manually determine 3D angular rotations and translations of the breast that occurred between acquisitions. One image set was rigidly transformed to better align the two image sets. A registration method developed by Althof et al. was implemented to align and subtract ROIs in the two image sets using cross correlation[8]. An image 1 ROIs could be matched with any ROI in image 2 within a certain volume of data (340μmx340μm x12mm). This was done in an attempt to limit the area of registration to a region that was most likely to contain the corresponding match. Angular rotations of the ROI ±15° were also explored in order to match the ROIs more effectively.

A subtle round mass was simulated in the images in an attempt to highlight significant temporal change between acquisitions. To minimize potential mis-registration, the algorithm was run twice to find the "ideal" ROI to subtract and then again, to subtract the ROI with the simulated lesion from its best matched ROI in image set 1. Although constraints were implemented to disregard registering to image noise, there were too many inter-image variations to adequately align the breast ROIs properly. If the overarching image gradients matched, there were still shading differences that appeared to increase the subtracted image contrast rather than decreasing it as expected. In addition, there were many ROIs that did not adequately match up with a corresponding ROI. An overwhelming number of ROIs adequately registered, however they were incorrect matchings in inappropriate locations and reflected a failure of the matching algorithm. These ROIs further increased image contrast because of incorrect registration issues.

As an example of how the registration of temporally sequential tomosynthesis images may appear, Figure 5 shows example input images and final results from our method. Figure 5a shows slice 17 from the original image set 1 and Figure 5b shows slice 17 from the rotated image set 1. Comparison of these two figures illustrates how the dataset was transformed to register more similarly to image set 2. Figure 5c shows slice 18 from image set 2, which is the slice that visually corresponds with slice 17 from rotated image set 1. Figure 5d is used to show which ROIs from image set 1, were used to subtract from image set 2. It is obvious that there is missing information as well as incorrectly registered ROIs. This mis-registration is demonstrated in the final subtraction result shown in Figure 5e. There are ROIs that appear to have subtracted similar breast texture, however these are still not perfectly aligned and creates increased contrast in the subtraction.

The addition of a simulated subtle mass was not visible in the resulting subtraction. This method did not show any increase in lesion conspicuity, most likely due to the overwhelming amount of mis-registered ROIs and severely dissimilar registered ROIs.
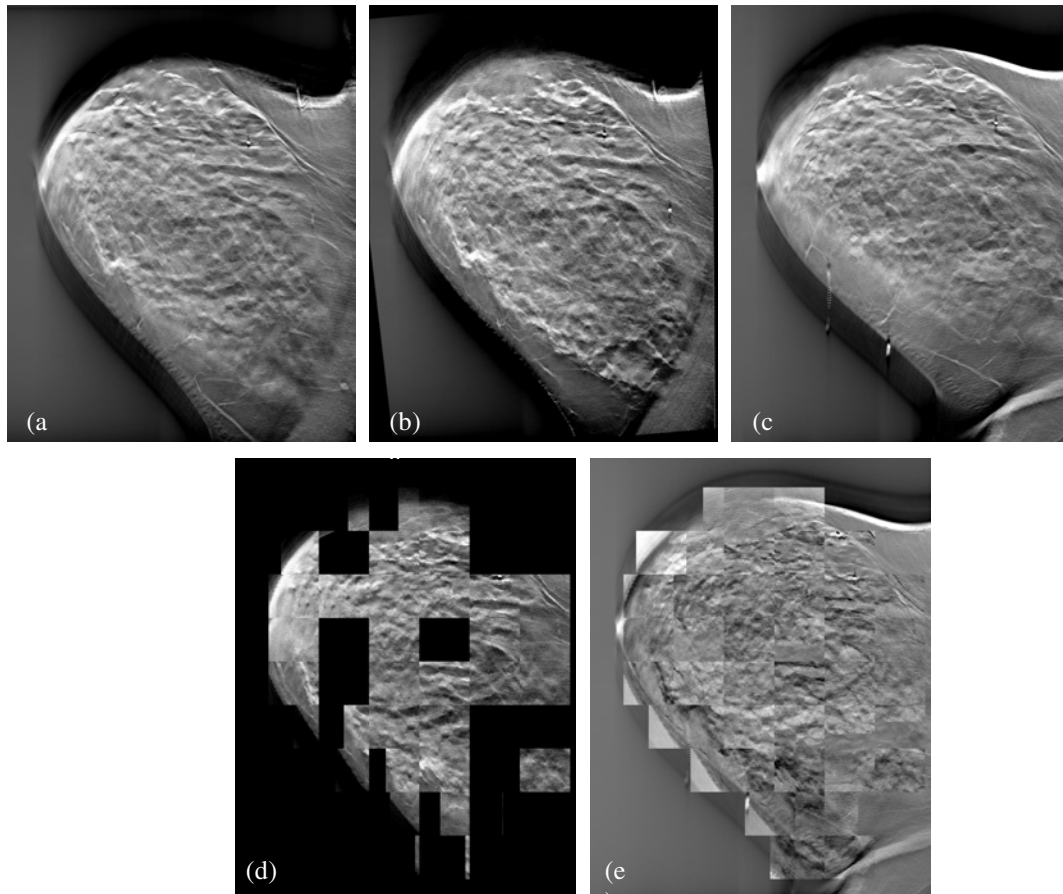
Figure 5: (a) An original slice from image set 1. (b) The same slice from a rotated image set 1. (c) An original slice from image set 2 that visually corresponds well to the top center image. (d) The collection of ROIs from image set 1 which registered to the slice from image set 2. (e) The result of the subtraction.

Issues: The major complication for registration of the two datasets is primarily due to differences in positioning and compression between the temporally spaced acquisitions. This caused structural discrepancies that created slight anatomical variations between reconstructed slices to significantly reduce registration ability and subtraction. The non-isotropic resolution of the imaging data did not allow for in-between plane information to be factored into the mechanical transformation algorithm. This contributed to incorrect registration issues since information between planes, did not get transformed onto a plane, and was not available for registration.

Fully 3D imaging data sets may increase the feasibility of this technique. However, although non-linear tissue warping techniques were not yet implemented, this work has demonstrated that the temporal subtraction of DBT images of human subjects is most likely infeasible. Therefore, moving forward the investigator will focus on the specific aim specified in Task 1a, the creation of a realistic computerized breast phantom.

Key Research Accomplishments

- An algorithm for the temporal subtraction for DBT human datasets was developed and implemented
- Results from human data shows that temporal subtraction of DBT data may be infeasible.
- Realistic computerized breast phantom development showed promising results
    - Dedicated breast CT data of human subjects was processed
    - An automated segmentation algorithm was developed
    - Mesh-surface model was created of all tissues
    - Simulated projection images were acquired of a single breast model
    - Compression algorithm must be made more realistic using finite-element methods.

Reportable Outcomes

1. **C. M. Li**, W. P. Segars, J. Y. Lo, et al., "Three-dimensional computer generated breast phantom based on empirical data," Medical Imaging 2008: Physics of Medical Imaging **6913**, 691314 (2008).
2. Oral presentation SPIE Medical Imaging 2008.
3. McAdams H.P., Dobbins J.T., III, **Li C.M.**,"Digital Tomosynthesis of the Chest for Lung Nodule Detection: Initial Clinical Experience," RSNA 93rd Scientific Program (2007).
4. Dobbins J.T., III, McAdams H.P., Godfrey D.J., **Li C.M.**, "Digital Tomosynthesis of the Chest," Journal of Thoracic Imaging 23, 86-92, (2008).
5. Dobbins, J. T., III, McAdams, Song J., **Li C.M.**, Godfrey D.J., DeLong D.M., Paik S., Martinez-Jimenez, S., "Digital tomosynthesis of the chest for lung nodule detection: Interim sensitivity results from an ongoing NIH-sponsored trial," Medical Physics 35, 2554-2557, (2008).
6. Abstract accepted for SPIE Medical Imaging 2009. "Computerized 3D breast phantom with enhanced high-resolution detail."
7. Preliminary exam completed.
8. Attended and poster presentation at the DOD Era of Hope Conference.

Conclusions

The original goal for this project, developing a temporal subtraction algorithm for phantoms, would ultimately be used for human subject data. Therefore, access to real human data prompted the investigator to create a method to subtract temporally acquired digital breast tomosynthesis images of human subjects. The feasibility study presented in this report shows that this technique is unlikely to be successful, although non-linear warping techniques were not implemented. The subtraction artifacts are primarily due to differences in patient positioning and compression amounts as well as the non-isotropic resolution of the DBT data. In the future, investigation into the temporal subtraction technique may be warranted with fully 3D imaging data. The demonstrated infeasibility of using temporal subtraction on digital breast tomosynthesis images completes Task 2 and 3.

Although the original goal of the project may be infeasible based on our results using human subject data, the investigator will focus on one specific aim in Task 1, which is to develop a realistic computerized breast phantom. The investigator believes that the promising results shown with the current breast model has the potential to contribute significantly to breast imaging research for the advancements of detection techniques and technologies.

The methods developed for this project to date have enabled the creation of a realistic computer-generated breast phantom based on empirical data. The model developed, combines the realism of high-resolution voxelized data with the flexibility of a mathematical phantom. There are several issues remaining, such as: refining the segmentation method, developing a realistic compression algorithm, and combining information from several different breast models into a single breast phantom.

The ultimate end-goal of this project will present researches with a detailed breast phantom that is based on real human data and a number of unique properties not currently offered by other phantoms. We will provide a realistic breast phantom that includes the ability to simulate of a variety of sizes, compositions, and deformations.

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Appendix 1

1. **C. M. Li**, W. P. Segars, J. Y. Lo, et al., "Three-dimensional computer generated breast phantom based on empirical data," Medical Imaging 2008: Physics of Medical Imaging **6913**, 691314 (2008).

Three-Dimensional Computer Generated Breast Phantom Based on Empirical Data

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ABSTRACT

The goal of this work is to create a detailed three-dimensional (3D) digital breast phantom based on empirical data and to incorporate it into the four-dimensional (4D) NCAT phantom, a computerized model of the human anatomy widely used in imaging research. Twenty sets of high-resolution breast CT data were used to create anatomically diverse models. The datasets were segmented using techniques developed in our laboratory and the breast structures will be defined using a combination of non-uniform rational b-splines (NURBS) and subdivision surfaces (SD). Imaging data from various modalities (x-ray and nuclear medicine) were simulated to demonstrate the utility of the new breast phantoms. As a proof of concept, a simple compression technique was used to deform the breast models while maintaining a constant volume to simulate modalities (mammography and tomosynthesis) that involve compression. Initial studies using one CT dataset indicate that the simulated breast phantom is capable of providing a realistic and flexible representation of breast tissue and can be used with different acquisition methods to test varying imaging parameters such as dose, resolution, and patient motion. The final model will have a more accurate depiction of the internal breast structures and will be scaleable in terms of size and density. Also, more realistic finite-element techniques will be used to simulate compression. With the ability to simulate realistic, predictive patient imaging data, we believe the phantom will provide a vital tool to investigate current and emerging breast imaging methods and techniques.

Keywords: Breast Imaging, Phantoms, Simulation, Tomosynthesis, Computed Tomography

I. INTRODUCTION

Computer phantoms are becoming an essential tool for use in medical imaging research because of the difficulty in obtaining real human data because of subject recruitment issues and radiation dose considerations. Computer phantoms are advantageous in that they can be modified in terms of size and tissue distribution and they provide a known truth from which to evaluate imaging devices and techniques. The four dimensional (4D) non-uniform rational b-splines (NURBS) based Cardiac-Torso (NCAT)[1-5] phantom (Fig.1) was developed by Segars *et al* to provide a realistic and flexible anatomical and physiological model of the human torso for use in nuclear medicine research, specifically

SPECT and PET. The NCAT anatomy was originally based on the Visible Male CT dataset from the National Library of Medicine (NLM)[6, 7]. The anatomical detail of the NCAT phantom was recently enhanced and extended to include detailed structures from head to toe with the purpose of making the phantom applicable to high-resolution imaging modalities such as MRI and X-ray CT. The work included updating the original template for the male anatomy and the creation of a separate template for the female anatomy based on the Visible Female data from the NLM[6, 7]. Despite this advancement, the female anatomy of the NCAT phantom only uses a simple outer surface to model the breast and does not include any detailed structures. As a result, the NCAT is limited in its application to breast imaging research.
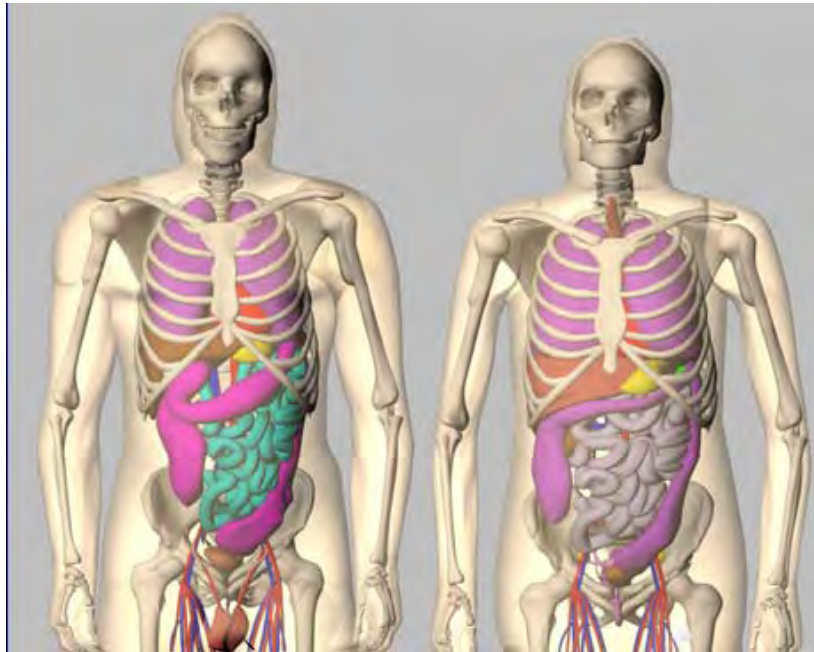

Figure 1: Surface renderings of the 4D NCAT male (left) and female (right) anatomy.

Breast imaging is an important area of research with many new techniques being investigated to further reduce the morbidity and mortality of breast cancer through early detection. There have been several computerized 3D breast phantoms created, all based either on voxelization of real subject data or mathematical models based on geometric primitives[8-22]. Bakic *et al* created synthetic x-ray mammograms using a 3D simulated breast tissue model consisting of glandular and adipose tissues as well as a ductal tree all undergoing a simulated mammographic compression deformation model[13-15]. Bliznakova *et al* utilized a combination of voxel matrices and geometric primitives to create a breast phantom that includes the breast surface, the duct system, and terminal ductal lobular units, Cooper's ligaments, the pectoral muscle, the 3D mammographic background and breast abnormalities. Simulated fan beam projections of the non-compressed phantom were used to generate mammographic images of different breast models and compared to real mammograms in order to evaluate how realistic the simulations appeared[16]. Hoeschen *et al* created a voxelized breast phantom, consisting of segmented skin, adipose, and breast tissue, from high resolution CT data of compressed breast specimens taken from cadavers for the purpose of mammographic dose calculations[17]. Zhou *et al* created a 3D breast phantom which included models of ductal structures, fibrous connective tissue, coopers ligaments, pectoralis muscle, lesions, and structural noise. Low dose tomosynthesis projections were simulated and reconstructed using 3 different algorithms to evaluate the detectability of masses under low-contrast situations[19].

The goal of this work is to create a detailed 3D computer generated breast phantom based on empirical data using a combination of NURBS and subdivision surfaces (SD). The phantom will be incorporated into the 4D NCAT phantom in order to make it applicable to breast imaging research.

II. METHODS

2.1 Image Acquisition and Reconstruction

Twenty high-resolution breast CT datasets were acquired with a prototype cone beam CT dedicated breast imaging system[23-27]. The imaging geometry utilizes a breast which is uncompressed and pendant. Five hundred projections were acquired with a total dose equivalent to dual-view mammography. The image quality of the CT reconstructions was degraded due to scatter radiation and considerable quantum noise due to the low dose used for acquisition. To correct for this, we used a method developed by a colleague to perform scatter and noise correction on the breast CT projection images prior to reconstruction with minimal loss of spatial resolution[28]. The original CT projections were reconstructed using this technique with a resolution of 400 μm. Figure 2 shows the original reconstructed CT data compared to a reconstruction performed using the denoising technique.
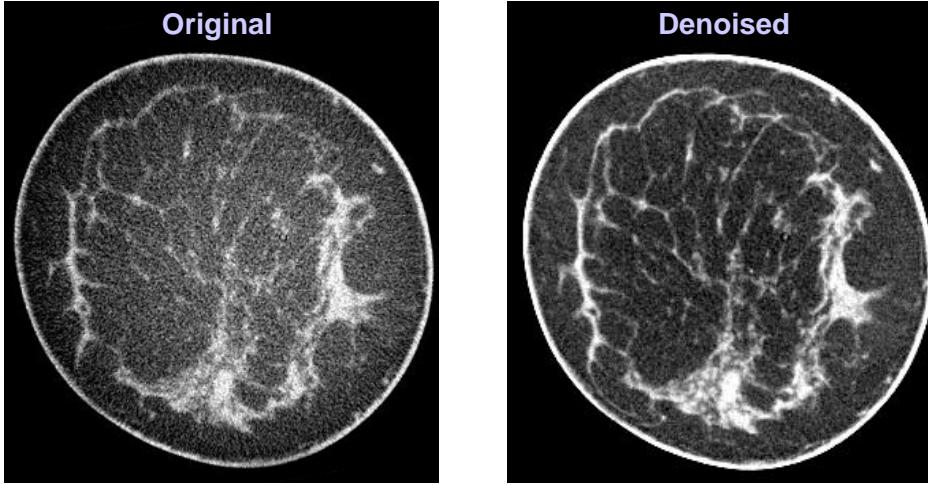

Figure 2: On the left is the original reconstructed CT data and on the right is the resultant denoised data which illustrates the algorithms ability for noise and scatter reduction.

2.2 Segmentation

To analyze the breast CT datasets, we developed a semi-automatic segmentation algorithm. The algorithm consisted of the following steps. The denoised data first underwent median filtering in order to further suppress noise that would degrade tissue classification. A mask was created by thresholding to remove the background from the data. Next, the local standard deviation of the dataset was found for a 3x3 neighborhood and then thresholded in order to segment the skin. The skin was then removed and then an initial segmentation of the adipose and fibroglandular tissue was done using K-means clustering with user-defined cluster centers. Region growing was implemented based on gray level values and a distance metric to extend the defined segmented areas to additional regions. Morphological operations were used to bridge gaps and fill holes to further connect the defined fibroglandular regions. Finally, obvious non-fibroglandular voxels that were mis-classified by the morphological dilation operations were removed in the final step based on their gray level values.

This method was used to segment a given CT dataset into 3 materials: skin, fibroglandular tissue, and fat (Fig. 3).
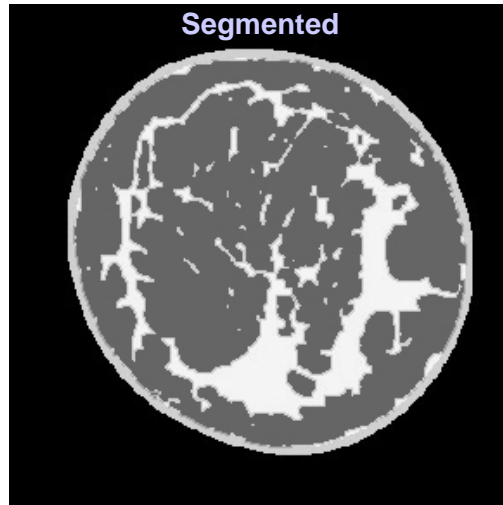
Figure 3: Slice from segmented volume, fibroglandular tissue is in white, skin is shown in light gray, and fat is in dark gray.

2.3 Phantom Development

A mathematical breast phantom was created by using a marching cubes algorithm on the segmented data to generate an initial polygon mesh. After undergoing a mesh optimization routine from the Visualization Toolkit (VTK), the resultant mesh was stored as an initial input to a subdivision surface[29] model to incorporate into the NCAT phantom. Figure 4 shows surface renderings of one breast phantom created based on the CT data.
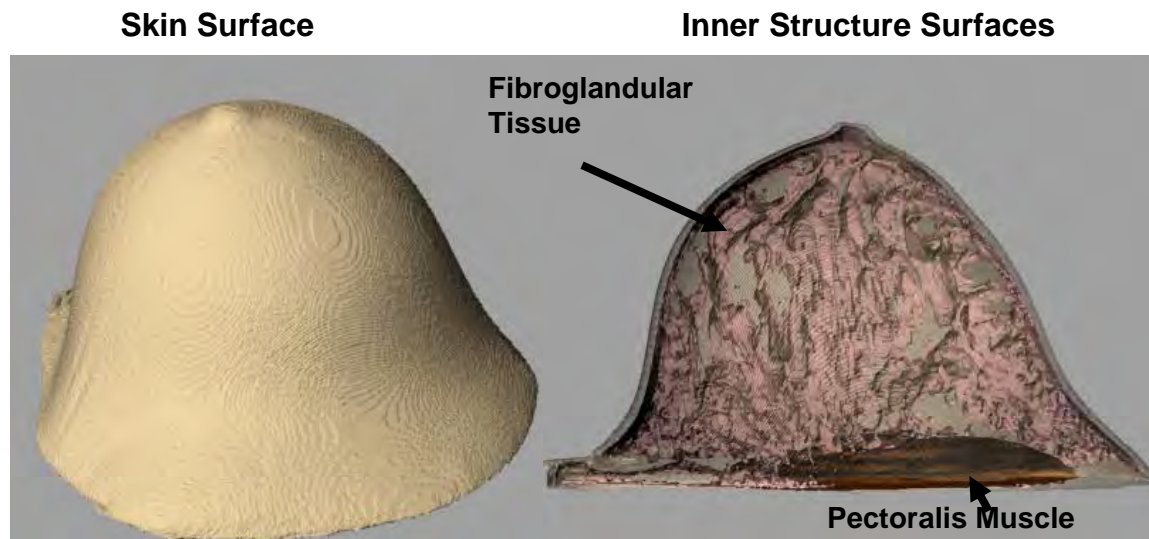

Figure 4: Surface rendering of the skin is shown on the left and a central slice illustrating the inner structures is on the right with the fibroglandular and pectoralis muscle shown.

2.4 Simulated Compression

As an initial proof of concept, a simple compression algorithm was implemented on the phantom to illustrate its flexible nature. The algorithm compressed in one dimension, simulating compression between stiff plates, and extends the breast in the other dimensions in order to maintain the same volume. The varying mechanical properties of the different tissues were not considered. We plan to utilize a more realistic finite-element based technique in the future.
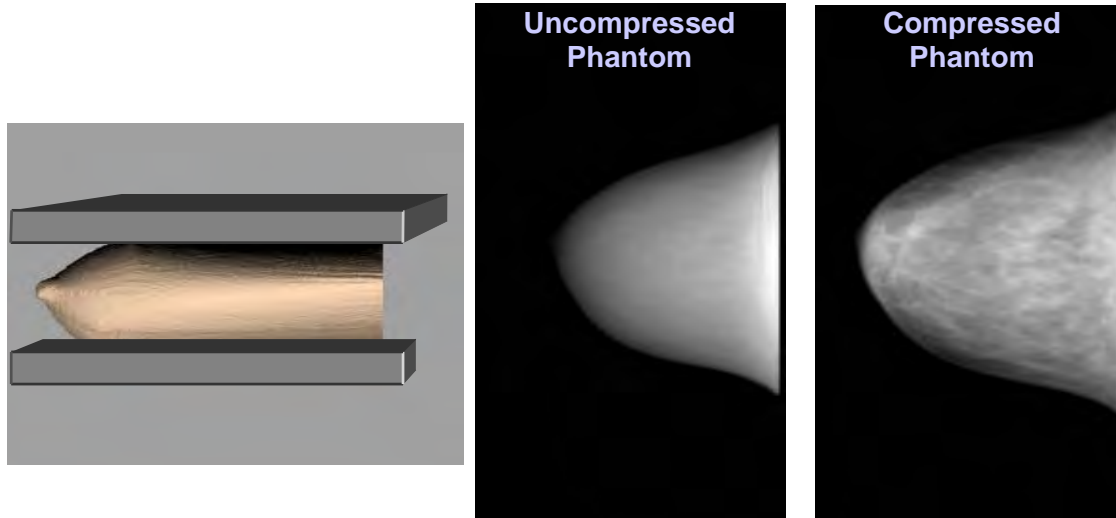
Figure 5: Left: Illustration of how our compression was performed. Middle: Projection of uncompressed breast. Right: Projection of compressed breast.

III. RESULTS

X-ray imaging systems were modeled as analytical noise free simulators[1, 4] in order to test how the computer simulated compressed breast phantom would appear during simulated mammography and tomosynthesis acquisitions.

For the mammogram acquisition, the cranio-caudal view was simulated and material characteristics for fibroglandular and skin tissues were chosen to be the same as muscle. A sigmoid output transform was applied to display the simulated image in an optimal manner.
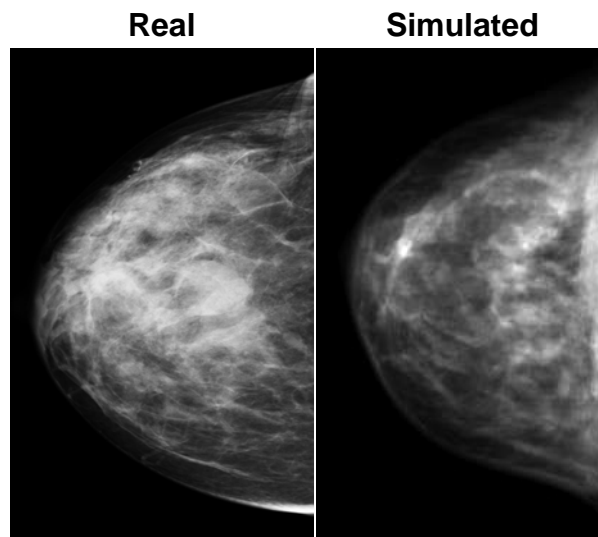

Figure 6: Comparison of real (Left) and simulated (Right) mammogram

For the tomosynthesis simulated acquisition, we modeled the geometry after the prototype Siemens Mammomat Novation[TOMO] system, simulating 25 projections acquired over 45°. The fibroglandular and skin tissues were again defined to have the same material characteristics as muscle and 21 keV was used to define their attenuation characteristics. The final simulated tomosynthesis dataset was reconstructed with Seimens' proprietary filtered-back-projection algorithm[30]. Figures 6 and 7 show a comparison of simulated results to those obtained from human subjects. The simulated results compare very favorably to the human subject images. However, there are some artifacts due to the surface sub-sampling in our model, as well as some issues due to the low resolution of our simulated image acquisition. These issues will be addressed in future work.
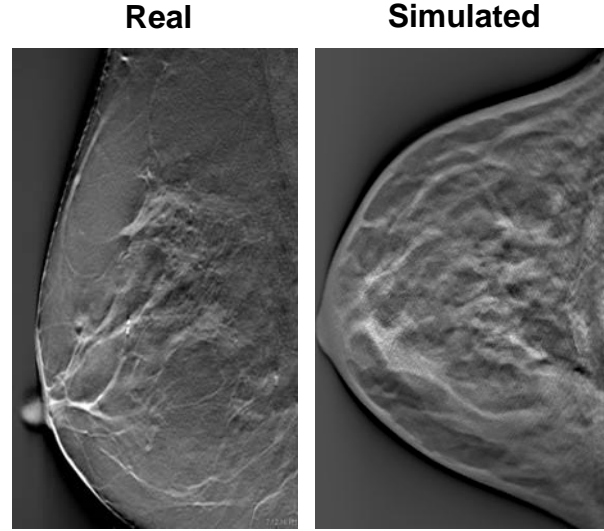
Real   **Simulated**

Figure 7: Comparison of real (Left) and simulated (Right) tomosynthesis reconstruction.

In addition to x-ray modalities, the breast phantom also has application in nuclear medicine (PET and SPECT). To illustrate this, we generated SPECT data of the breast phantom simulating the uptake of Tc-99m Sestamibi. For this simulation, we included an 8 mm diameter spherical lesion with an uptake ratio of 10:1 relative to the background. The reconstructions were done using a 140 keV attenuation map to correct for effects due to attenuation. Figure 8 shows the breast phantom as used to simulate SPECT imaging data. Similar methods can be done to simulate PET imaging data.
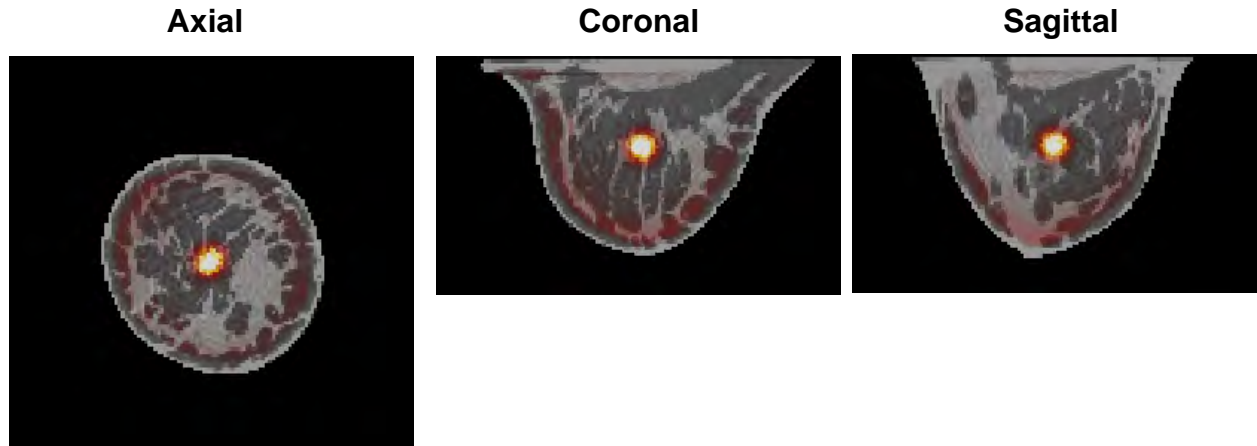
Axial   **Coronal**   **Sagittal**

Figure 8: SPECT images are shown overlaid on a 140 keV transmission image.

IV. DISCUSSION

In this work, we developed an initial breast phantom based on empirical data and tested the feasibility of using it to simulate various breast imaging modalities. We developed methods to efficiently segment breast CT imaging data and to define 3D models for the detailed structures within the breast. These methods form the basis for future work. The segmentation algorithm will be further refined in order to account for high frequency texture detail which is not currently visible. The surface modeling will be further refined in order to remove any sub-sampling artifacts. We will also use finite element techniques[31-33] which take the different material mechanical properties of the different breast tissues into account in order to accurately model realistic breast compression. Figure 9 shows an example of how we plan to use finite element techniques to simulate breast compression. The final breast models incorporated into the NCAT phantom will have a more precise representation of the internal breast structures and will be scaleable in terms of size and density.

Figure 9: Example of using finite element model to compress the breast outer surface.

We conclude that the incorporation of a detailed breast model into 4D NCAT will provide an important tool in breast imaging research. It has the potential to be quite useful in the investigation of current and emerging techniques used in the diagnosis of breast cancer.

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